REMARKS

STATUS OF THE CLAIMS

Claims 1-2, and 4-20 were pending in this application. Claims 1 and 11 have been amended, and claim 21 has been added. Following entry of the amendments claims 1, 2, 4-21 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claims 1 and 11 have been amended so that the compound specifically hybridizes with a target defined by nucleotides 391 through 1639 of the nucleic acid molecule encoding human interleukin 8 (SEQ ID NO:3). The amendment more clearly defines Applicants' invention. Support for the amendment can be found throughout the specification as filed, e.g., SEQ ID NO:3 recited on page 80, lines 21-26, and the compounds disclosed in Table 1 of the specification that hybridize to the nucleotide ranges recited by amended claims 1 and 11.

Claim 21 has been added, and is a modified version of original claim 3, wherein all recited SEQ ID NOS hybridize to nucleotides 391 through 1639 of the nucleic acid molecule encoding human interleukin 8 (SEQ ID NO:3). The amendment finds support in the claims as originally filed.

The amendments to the claims therefore add no new matter.

RESTRICTION REQUIREMENT

In the Office Action dated September 26, 2003, the Examiner stated that the Response filed 07/07/03 (mistakenly identified as the amendment filed on April 30, 2003) was not fully responsive to the prior Office Action because "the entirety of applicants' response is dependent on claims encompassing multiple distinct target regions that are considered to be unrelated for reasons of record." The Examiner directed Applicant to select one target sequence or one antisense sequence from the instant claim set.

In response, Applicant has submitted newly amended claims 1 and 11, directed to a compound targeted to nucleotides 391 through 1639 of SEQ ID NO:3. As these amended claims recite only one target sequence, restriction is not required.

In response to a request to select one antisense sequence, Applicant hereby elects without traverse SEQ ID NO:58 of new claim 21. Based on the interview with the Examiner, Applicant believes that the restriction of claim 21 is subject to the non-allowance of linking claims 1 and 11.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 11 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey that the applicants had possession of the claimed invention.

The applicants traverse the rejection. In Example 15, page 80, line 16 to page 83, line3, the applicants provide detailed instructions on how to determine the "active site". Table 1 lists sequences that are complementary to the "active site" and are therefore the preferred sequences. The test the applicants need to meet in order to satisfy the requirements of 35 U.S.C. §112, first paragraph is whether one of skill in the art would understand that the applicants had possession of the invention at the time of application. It is axiomatic that compliance with the written description requirement of 35 USC §112, first paragraph only requires that the application contain sufficient disclosure, either expressly or inherently, to make clear to persons skilled in the art that the applicants were in possession of the subject matter claimed. See, e.g., *In re Mott*, 190 USPQ 536, 541 (CCPA 1976); and *Ex parte Harvey*, 3 USPQ2d 1626, 1627 (BOPAI 1987). By providing detailed instructions and providing an extensive list of sequences that are directed towards the "active site" the applicants have met the test to satisfy the written description requirement. The Examiner is respectfully requested to withdraw the rejection.

Claims 15-20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner acknowledges that the "specification teaches a method of using the claimed compositions to inhibit the suppression of interleukin-8 cells in vitro" (page 4, last line of the first paragraph of the Office Action under reply). However, the Examiner argues that the specification does not provide guidance for the in vivo environments.

The test for enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." United States v Telectronics, Inc. 8 USPQ2d 1217 (Fed. Cir. 1988); In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988). Thus, in order to satisfy Section 112 regarding enablement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The burden is on the Office to explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Office has failed to provide adequate evidence to support the present rejection. Without such evidence, a rejection under 35 U.S.C. §112, first paragraph for lack of enablement cannot be sustained.

The term "*in* vivo" is art recognized to mean a biological or biochemical process occurring within a living organism, while "*in* vitro" means a biological or biochemical process occurring outside a living organism. The specification, in Example 9 describes the use of four different cell types (T-24, A549, NHDF cells, and HEK cells) to measure the effect of antisense compounds of the invention on the expression of IL-8 gene. Examples 10 and 13 describe the use of real-time quantitative PCR to measure oligonucleotide inhibition of IL-8 expression, while Example 16 describes the use of Western blot analysis of IL-8 protein levels in cells. The applicants have thus provided examples of methods of inhibiting the expression of IL-8 in cells or tissues as claimed in claim 15. Further, the applicants' specification and examples are detailed enough that one of skill in art could follow the disclosed protocols to determine if the expression

of IL-8 was inhibited *in vivo* for another cell type or an animal without undue experimentation. Therefore, the invention of claims 15-20 is enabled. The Examiner has provided no reason to doubt that the invention is not enabled. Therefore, the Examiner is respectfully requested to withdraw the rejection.

REJECTIONS UNDER 35 U.S.C. § 102/103

A. Claims 1-2, 4-20 are rejected under 35 U.S.C. 102(b) and 103 (a) as being anticipated and/or obvious by any of Blaser et al. (U.S. Patent Number 5,527,678), Daly et al. (U.S. Patent Number 5,789,539), Emmett et al. (WO 96/39536), or Malefyt et al. (U.S. Patent Number 5,833,976). Applicants traverse this ground of rejection by amendment and argument.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Claims 1 and 11, as amended, recite that the compound specifically hybridizes with a target region defined by nucleotides 391 through 1639 of the nucleic acid molecule encoding human interleukin 8. The cited references do not disclose any compounds that would hybridize with the selected regions of IL-8 of SEQ ID NO:3. The references thus do not disclose all the limitation of the claimed invention. Therefore, the Examiner is respectfully requested to withdraw this rejection.

B. The Examiner has rejected claims 1, 2, 4, 5, 8, 9, and 12-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Nyce, J (WO 99/13886). The applicants traverse the rejection. The reference discloses multi-target oligonucleotides that are modified to make them incapable of activating adenosine receptors. The reference, at page 6, lines 19-26, states that the oligonucleotides are targeted to mRNA. The disclosed sequences are not complementary to SEQ ID NO:3, therefore one would not expect them to specifically hybridize to SEQ ID NO:3. The cited reference does not state the oligonucleotides could specifically hybridize to nucleic acid molecules encoding human interleukin 8 and inhibit its expression. Further, the Examiner has not shown that the fragments disclosed on page 55, lines 37-60, of the cited reference are capable of hybridizing to IL-8 of SEQ ID NO:3. Thus, Nyce does not disclose all the elements of

the claimed invention, and, therefore, does not anticipate the applicants' invention. The Examiner is respectfully requested to withdraw this rejection.

C. Claims 1, 2, and 15 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Arici et al. (J. Clin. Endocr. and Metab., 1998. 83(4) 1201-5). The reference discloses two antisense compounds, AS-I and AS-II, which are not included within the scope of the independent claim 1 as amended. The Examiner is respectfully requested to withdraw this rejection.

D. Claims 1, 2, and 12-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Pietrzkowski et al. (U.S. Patent Number 6,017,898). SEQ ID NO:4 of the reference is not included within the scope of the independent claim 1 as amended. The Examiner is respectfully requested to withdraw this rejection.

E. Claims 1, 2, and 15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Miyamoto et al. (Canc. Immunol. Immunother. (1998) 47:47-57). The reference discloses two antisense compounds, AS1 and AS2, which are not included within the scope of the independent claim 1 as amended. The Examiner is respectfully requested to withdraw this rejection.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over either Matsushima *et al.* (J. Exp. Med. 167:1883-1893, 1988), Arici *et al.*, Pietrzkowski *et al.*, Miyamoto *et al.*, or Nyce *et al.* in view of Taylor *et al.*, and Baracchini *et al.* Applicant traverses this ground of rejection by amendment and argument.

Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The cited prior art references do not teach all of the elements of the claims. As acknowledged by the Examiner, the primary reference Matsushima *et al.* discloses a cDNA sequence that is 78 nucleotides shorter than the applicants' SEQ ID NO:3. The Federal Circuit in Fiers v. Revel 25 USPQ2d 1601 (1993) stated "if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is until after gene has been isolated; ... conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility." The reference discloses functional utility of the sequence as encoding for IL-8, however, the disclosed nucleic acid molecule is different than the one claimed by the applicants. Therefore, it does not disclose all the elements of the claims.

Further, Arici *et al.*, Pietrzkowski *et al.*, Miyamoto *et al.*, or Nyce *et al.* are said to disclose antisense sequences for the inhibition of IL-8 expression. However, the scope of the independent claim 1, as amended, does not include sequences disclosed by the cited references. Accordingly, the combination of Matsushima with Arici, Pietrzkowski, Miyamoto, or Nyce does not include the element of a nucleic acid molecule encoding human interleukin 8 (SEQ ID NO:3), or a compound that specifically hybridizes with said nucleic acid molecule encoding human interleukin 8 and inhibits the expression of human interleukin. The combination cannot render the claims obvious.

The cited art does not teach or provide a motivation to combine the teachings. The motivation to combine is said to be provided by the modified antisense oligonucleotides having increased cellular uptake, target affinity and resistance to degradation. These are generalized scientific goals that cannot substitute for the particularity needed to establish a *prima facie* case of obviousness. The Examiner must show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458, 1453 (Fed. Cir. 1998). Thus, the motivation to combine must be

particularized, and the required evidence cannot be substituted with a generalized scientific goal, as the Examiner has done in the present case. At no point do the combined references disclose or suggest modified oligonucleotides that would specifically hybridize with SEQ ID NO:3 and inhibit the expression of human interleukin.

The particularity needed to establish a motivation to combine references was further discussed in *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002). In *In re Lee*, the Board had determined that it was not necessary to present a source of a teaching, suggestion, or motivation to combine the references because the conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art. The court reversed the Board of Patent Appeals and Interferences' decision and stated: "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent ... cannot be dispensed with. The need for specificity pervades this authority." The Federal Circuit further stated that omitting the need for a specific suggestion in a particular reference to support the motivation to combine was both a legal error and arbitrary agency action (at 1434). Thus, the generalized motivation to combine fails to rise to the level of particularity required by the Federal Circuit. In the present case, the Examiner has not met the required specificity to establish a motivation to combine the references.

In the absence of some teaching or suggestion in the cited references concerning the method of the present invention, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

In conclusion, the cited references do not disclose all the limitations of the claims, and there is not motivation to combine the references as suggested by the Examiner. Accordingly, a *prima facie* case of obviousness has not been presented by the Office. Therefore, withdrawal of this ground of rejection of claims 1, 2, 4-10, and 12-15 is respectfully requested.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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